NTP
National Toxicology Program

Toxicology and Carcinogenesis Studies of 1-Bromopropane in F344/N Rats and B6C3F1 Mice
(Inhalation Studies)

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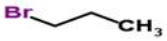
Technical Reports Subcommittee
November 19, 2009

1-Bromopropane (n-Propyl Bromide)



- **Nomination**: OSHA & NIOSH
  - Chronic toxicity and carcinogenicity by inhalation
  - Reproductive toxicity studies
  - Neurotoxicity studies
- **Rationale**:
  - Lack of toxicity and carcinogenicity data
  - Toxicity/carcinogenicity of other brominated alkanes
  - Anticipated increase in US production and use
  - Potential widespread human exposure

1-Bromopropane: Uses

- Substitute for restricted solvents:
  - Methyl chloroform, CFC-113, HCFCs, methylene chloride, PERC
- Highly emissive uses:
  - Metals, electronics and critical cleaning
  - Carrier solvent for aerosols
  - Carrier solvent in adhesives
  - Solvent in dry cleaning

Studies Conducted

- Genetic Toxicity
  - Bacterial mutagenicity test
  - Mouse micronucleus assay
- ADME Studies
- 2-Week Inhalation Studies
- 3-Month Inhalation Studies
  - SMVCE
  - Immunotoxicity
- 2-Year Toxicity and Carcinogenicity Inhalation Studies

Genetic Toxicity

Salmonella (Ames assay) - **Negative** +/- metabolic activation

Micronucleated erythrocytes - **Negative**

ADME Studies in Rats and Mice

IV injection, Inhalation, Dermal exposure to ^{14}C-labeled 1-BP

- Similar kinetics after intravenous and inhalation
  - Extensive tissue distribution
  - Rapid clearance from blood and tissues
  - Rapid elimination - exhalation in breath major route
  - Metabolism - primarily P450
  - Dermal - minimal absorption

Prechronic Studies In F344 Rats

2-Week: 0, 125, 250, 500, 1000, 2000 ppm

- 2000 ppm - Impaired gait, ↓ body wts, ↑ liver & kidney wts (♂ & ♀)

3-Month: 0, 62.5, 125, 250, 500, 1000 ppm

- 1000 ppm - ↓ body wts (♂), ↑ Liver wt; degeneration, vacuolization

Reproductive Parameters in F344 Rats (SMVCE)

3-Month Study: 0, 62.5, 125, 250, 500, 1000 ppm

- **Males**
  - ↑Wt of cauda epididymis, 14%; testis, 8% (1000 ppm)
  - ↓Sperm/cauda 37% (1000 ppm)
  - ↓Sperm motility: 7% (250 ppm), 10% (500 ppm), 28% (1000 ppm)
- **Females**
  - Estrous cycle effects at 250, 500, 1000 ppm
    - ↑Time in estrus
    - ↓Time in diestrus

Immunotoxicity Studies in Female Rats

3-Month Study: 0, 250, 500, 1000 ppm

- Concentration-related ↓ total splenocytes
- Concentration-related mild ↑ NK cells
- ↑ IgM response to SRBC @ 1000 ppm

Chronic Studies in Rats

Exposure Concentration Selection:

0, 125, 250, 500 ppm ♂ & ♀ rats

- Based on 3-mo study results:
  - Decreased body weights at 1000 ppm
  - Increased liver weights at 1000 ppm
  - Incidence and severity of hepatocellular degeneration and vacuolization at 1000 ppm

Chronic Studies in Rats

1-BP (ppm):	0	125	250	500
%Survival (male):	46	52	36	26*
%Survival (female)	68	66	60	50
Body Weights (%control)				
male	100	107	105	97
female	100	97	97	92

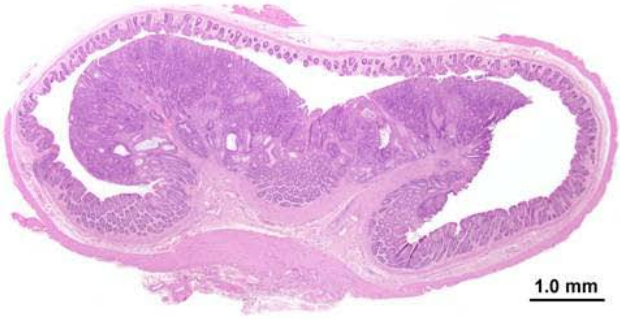
Neoplastic Lesions in Rats

Intestine, large: adenoma (colon/rectum)

1-BP (ppm):	0	125	250	500
Males	0	0	2 (5%)[a]	1 (3%)
Females	0*	1 (2%)	2 (5%)	5 (13%)*

HC inhalation: 0%
HC all routes: 0 - 2%

[a] Adjusted rates



Neoplastic Lesions in Rats

Skin, keratoacanthoma

1-BP (ppm):	0	125	250	500
Males [a]	0*	3 (7%)	6 (15%)*	6 (16%)*

Skin; keratoacanthoma, basal cell adenoma/carcinoma or squamous cell carcinoma

1-BP (ppm):	0	125	250	500
Males [b]	1 (2%)*	7 (17%)*	9 (23%)*	10 (27%)*
Females [c]	1 (2%)*	1 (2%)	1 (2%)	4 (11%)

[a] HC inhalation: 0 - 8%, all routes: 0 - 16%
[b] HC inhalation: 0 - 10%, all routes: 0 - 20%
[c] HC inhalation: 0 - 2%, all routes: 0 - 6%

Neoplastic Lesions in Rats

Malignant Mesothelioma

1-BP (ppm):	0	125	250	500 ppm
Males [a]	0*	2 (5%)	2 (5%)	4 (11%)*

Pancreatic islets, adenoma

1-BP (ppm):	0	125	250	500 ppm
Males [b]	0*	5 (12%)*	4 (10%)*	5 (14%)*

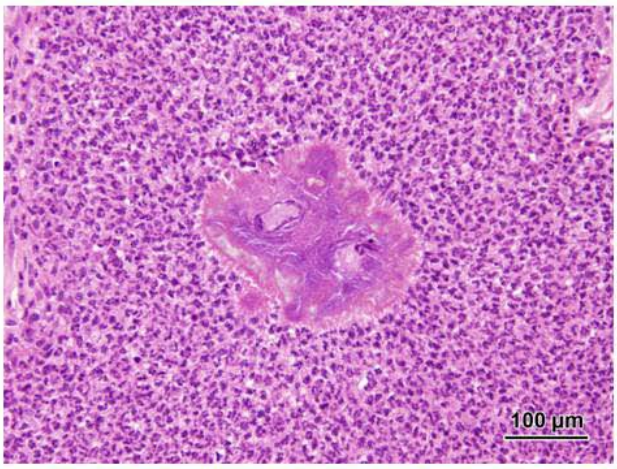
[a] HC inhalation: 0 - 6%, HC all routes: 0 - 6%
[b] HC inhalation: 0 - 12%, HC all routes: 0 - 14%

Nonneoplastic Lesions in Rats

- **Nose**
  - Suppurative chronic inflammation (with intralesional S-H bodies)
  - Hyaline droplet accumulation
  - Submucosal glands hyperplasia mild-mod
  - Hyperplasia of respiratory epithelium
  - Respiratory metaplasia of olfactory epithelium
- **Larynx**
  - Suppurative chronic inflammation (with intralesional S-H bodies)
  - Squamous metaplasia
- **Trachea**
  - chronic active inflammation

Splendore-Hoeppli Bodies

- Radiating eosinophillic deposits (starbursts) which form around fungi, helminths, or bacterial colonies
- Composed of cellular debris and antigen-antibody precipitates
- Associated with immunosuppression or immune dysfunction
  - Corticosteroid treatment
  - Immunoglobulin deficiency
  - AIDS
- Typically present at sites of inflammation along with eosinophils, histiocytes, giant cells, etc.



Splendore-Hoeppli Bodies in Chronic Study

- Only present in exposed rats
- Concentration-related incidence
- Associated with chronic suppurative inflammation
  - Primarily nose and skin (13 different tissues)
- Marked severity in all exposed groups
- Lesions positive for *Pseudomonas aeruginosa*

Conclusions: F344 Rats

- **Some evidence of carcinogenicity in male rats** based upon the occurrence of adenomas of large intestine and increased incidences of neoplasms of the skin
  - Malignant mesothelioma and pancreatic islet adenoma may have been related to 1-BP exposure
- **Clear evidence of carcinogenicity in female rats** based upon the increased incidence of neoplasms in large intestine
  - Increased incidences of neoplasms of the skin may have been related to 1-BP exposure
- Treatment-related nonneoplastic lesions were present in the nose and larynx in males and females and in the trachea in females
- Spendore-Hoeppli bodies associated with suppurative inflammation were present primarily in nose and skin of males and females

Prechronic Studies In B6C3F1 Mice

2-Week Study: 0, 125, 250, 500, 1000, 2000 ppm

- 2000 & 1000 ppm - early deaths (♂ & ♀)

3-Month Study: 0, 62.5, 125, 250, 500 ppm

- 500 ppm - early deaths: ♂ (4/10), ♀ (5/10)
  - Liver: chronic inflammation, vacuolization; ↑liver wt
  - Nose: vacuolization of respiratory epithelium
- 62.5 to 500 ppm
  - Lung: bronchiolar necrosis, regeneration (minimal)

Reproductive Parameters in B6C3F1 Mice (SMVCE)

3-Month Study: 0, 62.5, 125, 250, 500 ppm

Males

- ↑ Relative wt of cauda epididymis: 12% (250 ppm), 20% (500 ppm)
- ↓ Sperm motility: 4% (250, 500 ppm)
- ↓ Sperm/mg cauda: 28% (500 ppm)

- **Females**
  - ↑ Cycle length (500 ppm)
  - ↑ Time in estrus (250 ppm)
  - ↑ Time in diestrus (500 ppm)

Immunotoxicity Studies in Female Mice

3-Month Study: 0, 125, 250, 500 ppm

- Concentration-related ↓ total splenocytes
- Concentration-related mild ↑ NK cells
- Concentration-related ↓ IgM response to SRBC

Chronic Studies in B6C3F1 Mice

Exposure Concentration Selection:

0, 62.5, 125, 250 ppm ♂ & ♀ mice

- Based on 3-mo study results:
  - Mortality at 500 & 1000 ppm
  - Changes in organ weights at 500 & 1000 ppm
  - Incidence and severity of nonneoplastic lesions of respiratory tract and liver at 500 and 1000 ppm

Chronic Studies in Mice

1-BP concentration: 0 62.5 125 250 ppm

- No treatment-related effects on survival
- No treatment-related effects on body weights

Neoplastic Lesions in Mice

Alveolar/bronchiolar adenoma or carcinoma

1-BP (ppm):	0	62.5	125	250
Females	1 (2%)*	9 (19%)*	8 (18%)*	14 (29%)*

HC inhalation: 2 - 12%, HC all routes: 2 - 18%

Nonneoplastic Lesions in Respiratory Tract of Mice

- **Nose**
  - Respiratory epithelium: vacuolization, hyperplasia
  - Olfactory epithelium: atrophy, respiratory epithelial metaplasia
- **Larynx/Trachea**
  - Respiratory epithelium: vacuolization, hyperplasia
- **Lung**
  - Bronchial epithelium: vacuolization

Conclusions

- **No evidence of carcinogenicity in male mice**
- **Clear evidence of carcinogenicity in female mice** based upon the increased incidence of alveolar/bronchiolar neoplasms
- Treatment-related nonneoplastic lesions were present in the nose, trachea and lungs in males and females, and in the larynx of males

Overall Evidence of 1-BP Carcinogenicity

- Some evidence - male rats
- Clear evidence - female rats
- No evidence - male mice
- Clear evidence - female mice